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## Comparative Effectiveness Research/Health Technology Assessment (HTA) Evaluation of Patient Registries Supporting Reimbursement Decisions: The Case of Oxaliplatin for Treatment of Stage III Colon Cancer



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### ABSTRACT

**Background:** Access with evidence development has been established for expensive intramural drugs in The Netherlands. The procedure involves a 4-year period of conditional reimbursement. During this period, additional evidence has to be gathered usually through a patient registry. Given the costs and time involved in gathering the data, it is important to carefully evaluate the registry. **Objectives:** This study aimed to develop a model for the regular evaluation of patient registries during an access with evidence development process and find the optimal length of the registry period. **Methods:** We used data from a recent registry in The Netherlands on oxaliplatin as a treatment option for stage III colon cancer. We added simulated follow-up data to the empirical data available and applied value of information analysis to balance the gains of extending the period and amount of data gathering against the costs of registering patients. **Results:** We show that given

the assumptions on cohort size, follow-up time, and purpose of the registry, the current (partly simulated) registry was not very efficient. Notably, the observation period could have been stopped to make a definite reimbursement decision after a maximum of 2 years rather than the fixed 4-year period. **Conclusions:** Patient registries may be an efficient way to gather data on new medical treatments, but they need to be carefully designed and evaluated, in particular regarding their follow-up time. For each purpose, data gathering can be tailored to make sure decisions are taken at the moment that sufficient data are available. **Keywords:** access with evidence development, decision theory, patient registry, reimbursement, value of information.

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### Introduction

The uncertainty in costs and effectiveness of new medical technologies makes it risky for decision makers to decide on reimbursement right after their market approval by authorities. However, it is essential to keep pace with the rapid development in the field of medical innovations. In recent years, the concept of “access with evidence development” (AED) has been introduced as a policy option to balance the careful evaluation of new technologies with improvements in patient care by rapid access to technologies.

In The Netherlands, conditional reimbursement has been implemented as a way to ensure access while new evidence is being gathered. The current regulation is still under development, but previous regulation included a period of 4 years [1] in which the drug was reimbursed under the condition that during this period sufficient information on its cost-effectiveness would be obtained. After the collection of data in this period, the cost-effectiveness of the drug is to be reassessed to make a definite

reimbursement decision. Given the rather ad-hoc decision on the 4-year period (it actually was 3 years originally), the question arises how long should the period of additional data gathering last; that is, what is the best time for reevaluation? It seems obvious that this will depend on the condition and the drug at stake. That is, efficiency improvements must be possible over and above the standard 4-year evaluation period. This is the focus of the present study.

Although randomized controlled trials are considered the criterion standard for gathering data on drug (cost-) effectiveness, patient registries are more attractive in conditional reimbursement settings. This is because additional clinical trials are difficult to organize in the same population in which a new medication is already adopted and reimbursed, even conditionally. Ideally, a formal value of information (VOI) analysis, along with full information on costs and expected outcomes of all possible forms of research, would inform the choice of an optimal research design [2]. The research decision space could also be

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widened by incorporating sequential VOI analysis and finding the best research design [3]. Perhaps the most efficient way of gathering additional data would be using an optimal portfolio of research combining different types of study designs including trials, epidemiological studies, surveys, and patient registries [4]. Staying closer to actual practice, however, registries are used without a VOI analysis being performed a priori.

Because of lack of randomization, registries have a serious risk of biased outcomes. This limitation may be managed to some extent by good design [5] and using analysis techniques such as propensity scores [6]. Because the present study is an example to illustrate how our methods for timing the reassessment and data-gathering period may work, these techniques were left aside.

Advantages of registries are that these reflect daily practice more closely and can include a larger population than do randomized studies because these do not require patients to agree to randomization for their treatment. Therefore, registries may be important sources of evidence [7].

The current research hence focuses on patient registries as the source of additional data gathering. Setting up and maintaining a registry is usually costly and time consuming, and so it is important to evaluate its added value, both in advance and during the registry period. If a registry aiming to support a reimbursement decision does not produce, or is no longer producing information helpful for that decision, it is not worthwhile to further delay the definite decision. In some cases, it might even be better to stop the registry and to use other sources of data (e.g., international trials) instead, unless other purposes warrant its continuation.

Although the registry helps to gain new information and hence to reduce the uncertainty in the decision, it imposes costs consisting of set-up costs and costs of registering patients. Moreover, during the conditional reimbursement period, no definite decision is taken and patients may receive suboptimal treatment as a result. In the Methods and Results sections, we explain how these may be balanced to evaluate the registry and find the best length for the period of additional data gathering. The discussion relates our findings to the actual data observation and decision process and considers how the process could be improved, changing the fixed 4-year period in the current regulations to a more flexible period.

## Methods

### Case Description

Our study concerns evaluating a registry used to support a reimbursement decision for the specific case study of third-line colon cancer treatment. We estimate the optimal duration of getting data from the registry. This duration could be very short or zero, actually indicating that the registry in its current form is not expected to add useful information for the decision concerning reimbursement. It might also be longer than actual follow-up, indicating that the follow-up time could have been longer to ensure a better decision.

Colon and rectal cancers are among the most common causes of death from cancer, with 447,000 new cases and 215,000 deaths in Europe in 2012 [8]. Since the 1990s, patients with stage III colon cancer were treated by adjuvant chemotherapy with 5-fluorouracil and leucovorin (5FU/LV) [9]. From 2005 onwards, National guidelines in The Netherlands have recommended the use of 6 months of treatment with 5FU/LV combined with oxaliplatin (FOLFOX) as the primary treatment option for patients with stage III and possibly high-risk stage II colon cancer. As an alternative, the use of capecitabine combined with oxaliplatin

(CAPOX) was also supported by the Dutch Association for Medical Oncology (Nederlandse Vereniging voor Medische Oncologie) [10].

Treatment costs with oxaliplatin are quite high; hence, the majority (80%) of oxaliplatin costs were reimbursed to hospitals in The Netherlands as of 2006 while a registry was initiated to provide additional information. This registry was set up to collect additional evidence during the conditional reimbursement period. It has also provided information on guideline implementation in daily practice with respect to treatment choice, patient characteristics, and dosage quantities [10]. The main question to be answered in the reevaluation was whether or not oxaliplatin should be allowed unconditional reimbursement. That is, the relevant comparisons were treatments including oxaliplatin versus treatments without oxaliplatin.

### General Approach

The evaluation of the registry was modeled using a wait-and-see process. In such a process, the data are observed over time and the model is updated using the observed data, until gathering more information is not worthwhile anymore. We assume that the data gathering can be stopped once the costs of the registry exceed the gains. Using a health care perspective, we assumed that the definite reimbursement decision would get informed by the distribution of incremental net benefits (INBs). The INB was calculated as  $\lambda \times (S_o - S_c) - (C_o - C_c)$ , where  $\lambda$  represents the willingness-to-pay threshold per disease-free life-day (DFLD) gained,  $S_o$  shows the DFLDs when using oxaliplatin (FOLFOX or CAPOX),  $S_c$  shows the DFLDs in the control population (5FU/LV or capecitabine), and  $C_o$  and  $C_c$ , respectively, are the total costs for both types of treatment. A positive INB value indicates that oxaliplatin is dominating the control treatment and is qualified for reimbursement. Starting with an initial distribution for INB at  $t_0$  (the starting point of the conditional reimbursement period), the distribution of INB was updated periodically using the registry data. In this way, the gain in information from the registry for the reimbursement decision was directly evaluated. Given disease prevalence and incidence, annual reevaluation was assumed. Patients included in the registry were diagnosed in the period 2005–2006; hence, the end of each year between 2006 and 2012 could have been a decision point (in 2012, the  $t = 4$  decision was scheduled, and almost all patients experienced a relapse). Having consecutive distributions of the INB, we calculated the gains obtained from the additional information after each year. Balancing these gains against the costs of the registry enabled us to evaluate the registry and decide on the optimal time of making a decision.

It must be noted that the current tool is intended to be used to optimize the time of a reevaluation, not to calculate a posteriori the value of a study. Hence, in actual practice, the method must be applied to prospective data.

### Patient Population

The registry data were gathered retrospectively during 2008–2009. The database includes 391 patients with stage III colon cancer receiving adjuvant therapy (see [10] for detailed inclusion criteria), of which 281 patients had been treated with oxaliplatin (FOLFOX in 136 patients and CAPOX in 145 patients). The remaining patients received capecitabine (93 patients) or 5FU/LV (17 patients). Follow-up time before a relapse or censoring was reported and used to estimate disease-free survival (DFS). Drug costs and follow-up costs were also registered [10].

### Prediction of Missing Data Values

Some patients did not have a relapse and were censored at the end of the data collection period. For the purpose of this study,

however, we need to consider the case in which the data would have been gathered beyond 2008–2009. Therefore, from 2009 onwards, simulation was used to project the remainder of each patient's lifetime. The simulation was based on Weibull distributions for DFLDs fitted to the available patient data. Using conditional survivals, the expected future life expectancies were computed for all patients (see [Appendix 1](#) in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2014.10.008>). Medical costs were observed for the period 2005–2008 and used to simulate treatment costs and follow-up costs for the remaining years. We used constant costs per day for the treatment phase and a gamma distribution on the proportion of total costs in each time interval during the follow-up phase, based on opinions of the involved experts (for more details, see [Appendix 2](#) in Supplemental materials found at <http://dx.doi.org/10.1016/j.jval.2014.10.008>). This resulted in a partly empirical, partly simulated database covering the periods 2005–2009 and 2010–2012, containing information on all patients diagnosed in 2005–2006.

### Survivals, Costs, and INBs

Because the purpose was to evaluate the registry at potential points of making a definite decision, we looked at the data at the end of each year as if there would be no more information available after that date. This mimics how the procedure could be used prospectively for a new decision, using a completely empirical database.

For each year, we filtered the (partly simulated) DFS to find the patients who had started treatment before the end of that year. If the patient experienced no event before the end of the year, the patient was censored for that year. The costs were simulated for all patients during their treatment and follow-up time. When a patient is censored, the costs up to the censor point were considered (see [Appendix 2](#) in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2014.10.008>).

This resulted in seven different data sets containing the data observed up to the end of each year. These were analyzed to find their overall mean and standard errors of survivals and costs, taking account of censoring.

Because of the severity of the condition, we assumed a rather large  $\lambda$  of €60,000/disease-free life-year gained ( $\sim$ €82/DFLD) in the base case. We changed this in the sensitivity analysis. The expected INB at the end of each year  $i$  was calculated as follows:

$$\text{INB}_i = (\lambda/365) \times [E_i(S_o) - E_i(S_c)] - [E_i(C_o) - E_i(C_c)] \quad (1)$$

where  $E_i(X)$  shows the mean of parameter  $X$  at the end of the year  $i$ . Assuming independency between costs and the DFS time, the squared standard error of  $\text{INB}_i$  then is

$$s.e.^2_{\text{INB}_i} = (\lambda/365)^2 \times [s.e.^2_i(S_o) + s.e.^2_i(S_c)] + [s.e.^2_i(C_o) + s.e.^2_i(C_c)] \quad (2)$$

This can be estimated for each year, using the number of patients in the registry at the end of each year ( $n_i$ ).

### Prior Distribution of INB

The distribution for INB at  $t_0$  (the start of the conditional reimbursement period) reflects the information available when the original decision to set up the registry was made. This distribution is called the prior distribution in a Bayesian analysis [11].

Using the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial [12], we found a mean and standard error for DFS days in each arm. Cost estimates used by decision makers at  $t_0$  were obtained from consultations with experts involved in the registry. We assumed that the additional costs of oxaliplatin per patient per treatment at  $t_0$  had a uniform distribution with parameters (€0, €25,000). Follow-up costs were equal for

treatment with or without oxaliplatin as an initial estimate. The expected INB and its standard error at  $t_0$  were then calculated as follows:

$$\text{INB}_0 = (\lambda/365) \times [E_0(\Delta S)] - [E_0(\Delta C)] \quad (3)$$

and

$$s.e.^2_{\text{INB}_0} = (\lambda/365)^2 \times (s.e.^2_0(\Delta S)) + (s.e.^2_0(\Delta C)) \quad (4)$$

where  $\Delta S$  and  $\Delta C$  indicate the additional survival and additional costs of oxaliplatin, respectively.

### INB Updates

Having a prior distribution for INB and expressions for its observation in each stage, we used a Bayesian approach to update the INB values after each stage, calculating the posterior by combining the prior with the information gathered during that stage. The new prior was then this posterior.

For notational simplicity, it is convenient to reexpress the standard errors as the precision:

$$\tau_i \equiv \frac{1}{n_i \times s.e.^2_{\text{INB}_i}} \quad i=0, 1, 2, \dots, t_m \quad (5)$$

where  $n_0$  is the number of patients in the initial trial (2246 in total [12]),  $t_m$  is the maximum time considered for the model, and  $n_i$  ( $i=1, \dots, t_m$ ) is the total number of patients in the registry in year  $i$ . After observing  $\text{INB}_i$ , the posterior of INB with respect to  $\text{INB}_i$  would be as follows [11]:

$$\text{INB} | \text{INB}_i \sim N \left( \frac{\tau_0}{\tau_0 + \tau_i} \text{INB}_0 + \frac{\tau_i}{\tau_0 + \tau_i} \text{INB}_i, \frac{1}{\tau_0 + \tau_i} \right) \quad i=1, 2, \dots, t_m \quad (6)$$

### Gains and Costs of Additional Follow-Up Time

At each potential decision point, the decision maker has the choice to stop getting observations from the registry and make the definite decision or to postpone the decision for one more year. The expected net gains (ENGs) of continuing the registry for one more year were found as the gains of waiting minus the costs of waiting.

### Gains as Expected Value of Sample Information

Gains of waiting for more evidence before making a decision were basically calculated as the reduction in opportunity losses (which are the health benefits forgone because of the use of suboptimal treatment) [13,14]. Making a definite reimbursement decision means that either oxaliplatin is going to be routinely prescribed together with 5FU/LV or capecitabine for all patients with stage III colon cancer in The Netherlands, or it would be completely removed from the list of reimbursed drugs. The expected value of sample information expresses the added value of gathering more information before taking the definite decision. The expected value of sample information at the end of stage  $i$  was computed as the reduction in the opportunity loss from the end point of stage  $i-1$  to the end point of stage  $i$ . The opportunity loss expresses the possible losses resulting from a wrong decision. When uncertainty in the INB distribution is low, the possibility of a wrong decision decreases and hence the opportunity losses also decrease. The reduction in opportunity loss could be found from changes in the distribution of INB after each stage. The detailed formulations of finding the opportunity losses and expected values of sample information are given in [Appendices 3 and 4](#) in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2014.10.008>.

### Number of Patients Who Benefit from the Decision

The number of patients in the country who can potentially benefit from a well-informed decision after each stage multiplied by the gain per patient gives the overall gain of continuation of



**Table 1 – Population parameters used in the model.**

Parameter	Value	Reference
Proportion of oxaliplatin users	0.7	The Dutch registry
Population of the country	16,000,000	–
Number of prevalent cases in 2006	8,300	[15]
Number of incident cases in 2006	1,900	[15]

the registry.  $N_i$ , the deterministic (observed) total number of patients at the end of year  $i$ , is calculated as follows:

$$N_i = N_{i-1} + (k \times P) - (r \times m_{\text{oxaliplatin}} \times N_{i-1} + (1-r) \times m_{\text{no oxaliplatin}} \times N_{i-1}) \quad (7)$$

where  $k$  is the incidence rate,  $P$  is the total population of the country,  $r$  is the proportion of patients who are using oxaliplatin, and  $m$  is the mortality proportion. For the application, prevalence and incidence rates of 2006 [15] were used to estimate the total number of patients benefiting from the decision at each stage ( $N_i$ ) (Table 1).

#### Costs of waiting

Costs of waiting include fixed costs of setting up the registry, which take place at  $t_0$ , and the variable costs of observing patients recruited over time. Therefore, at the end of the first stage, the total costs ( $tc_1$ ) would be

$$tc_1 = c_f + (n_{1o} + n_{1c}) \times c_v \quad (8)$$

where  $c_f$  is the registry set-up cost,  $c_v$  is the incremental variable cost per patient of being on the registry per year, and  $n_{1o}$  and  $n_{1c}$  are the number of registered patients for the first year in each group. From the second year onwards we have

$$tc_i = (n_{io} + n_{ic}) \times c_v \quad (9)$$

#### Gains versus Costs: ENG

Trading off the gains against the costs, the ENG of delaying the decision for one more year at the end of each year can be found. If the value of ENG turned out positive, this indicates that so far gains had been obtained from delaying the decision. If the value appeared negative (i.e., the cumulative ENG starts to decrease), the decision maker could stop the observation process because further continuation of the registry only implied more costs, unless the registry is providing gains for other purposes. Regardless of the latter, this would be the best time for the decision concerning definite reimbursement because further delay would add no value. This is a rule of thumb, based on the assumption that the cumulative ENG shows a single peak.

#### Sensitivity Analysis

The parameters related to the data and the update in INB were determined by the case study at hand, being outcomes of the

registry. Hence, for the sensitivity analysis, we focused on the parameters that were chosen by assumption. The willingness-to-pay threshold was varied between €20,000/disease-free life-year and €100,000/disease-free life-year.

The base-case value for the initial distribution of INB was based on the MOSAIC trial, which is an international multicounty study. We used a wide uninformative prior with the mean 0 to test how the results would change without any information available at  $t_0$ . Population statistics show that incidence and prevalence of stage III colon cancer are increasing. Hence, we also examined the effect of using the latest available data (i.e., data in 2012) on incidence and prevalence in The Netherlands.

## Results

### Simulating the Remainder of the Registry

The scale parameter(a) and the shape parameter (b) for the fitted Weibull distribution are presented in Table 2. Simulation of future disease-free lifetime shows that most patients would have had a relapse by the end of 2012. Please note that this simulation would be superfluous in case of an empirical registry with prospective decision making.

### Survivals, Costs, and INBs

Table 3 presents results for the survival as well as treatment costs at the end of each year, and the resulting INB. These figures are based on actual empirical data until 2008, and after that they are based on simulated data.

In the final years, because of a longer observation period, more disease-free days are observed and hence the mean is larger. Obviously, that does not imply that mortality is decreasing.

#### Prior Distribution of INBs

The DFS times of each arm and the incremental survival based on the MOSAIC trial [12] are reported in Table 4. Expected additional costs of oxaliplatin had been estimated to be €12,500 for a planned treatment of 6 months.

Using Equation 3 and the information available at  $t_0$ , the  $INB_0$  has the following distribution:

$$INB_0 \sim N(-7500, 1370^2) \quad (10)$$

### ENG of Additional Follow-Up Time

Monetary gains of waiting for each potential decision point are reported in Table 5. Fixed costs of registry set-up were by assumption €10,000 and the variable costs €200 per patient per year. Table 5 also reports the resulting values for ENG and their cumulative value after each year.

The gains of the registry when considering DFS and costs as outcomes never exceeded zero. The ENG quickly converged to a value of –77,400. This means that the registry did not resolve uncertainties around the INB nor reduced the risk of the decision (i.e., the opportunity losses). Such results indicate that if only DFS and costs are considered as relevant outcomes, getting data from the registry could better have been stopped after 1 year of observation.

### Sensitivity Analysis

Table 6 presents the results of the sensitivity analysis. Only a willingness-to-pay value of as high as €100,000/disease-free life-year gained implies a decision risk high enough to result in an

**Table 2 – Specifications of disease-free survival data based on the Dutch registry.**

Treatment	Survival days distribution
Oxaliplatin	Weibull* (1290.93)
No oxaliplatin	Weibull (14,303.4)
CDF, cumulative distribution function.	
* Weibull CDF ( $a, b$ ) of $1 - e^{-(x/a)^b}$ as the probability of event up to time $x$ .	

**Table 3 – Number of patients observed per arm, means and standard errors of disease-free survival days, costs, and INB using the data observed up to the end of each year for a willingness-to-pay value of €60,000/DFLY.**

Year	Number observed		Mean disease-free survival days (SE)		Mean costs (SE) (€)		INB (SE)
	Control	Oxaliplatin	Control	Oxaliplatin	Control	Oxaliplatin	
2006	103	260	640 (18)	590 (13)	5,800 (400)	17,900 (700)	–20,580 (870)
2007	110	280	920 (29)	840 (20)	8,300 (490)	21,000 (660)	–25,900 (970)
2008	110	280	1110 (43)	1020 (28)	9,800 (600)	23,000 (730)	–28,010 (1200)
2009	110	280	1150 (47)	1050 (31)	10,900 (720)	24,500 (810)	–30,650 (1350)
2010	110	280	1170 (49)	1050 (31)	11,100 (740)	24,600 (810)	–32,200 (1380)
2011	110	280	1170(50)	1050 (31)	11,200 (750)	24,700 (810)	–33,210 (1390)
2012	110	280	1170(50)	1050 (31)	11,200 (760)	24,700 (810)	–33,040 (1390)

DFLY, disease-free life-year; INB, incremental net benefit; SE, standard error.

optimal time of observation of 2 years. Assuming a very uninformative initial distribution for the INB with mean 0 rather than negative also results in an optimal time of 2 years. That is, in absence of information at the time of the conditional reimbursement decision, only 2 years of data observation would suffice for making a definite decision. Results for the prevalence and incidence rates indicate that the actual change in epidemiology of the disease during the period 2006–2012 did not affect the optimal time. Therefore, under the specific characteristics of this case study (without inflow of new patients into the registry), a maximum of 2 years of data observation appeared sufficient for informing a definite decision on reimbursement of oxaliplatin.

## Discussion

In this study, we evaluated the use of registry data to support the access with evidence process for the reimbursement of oxaliplatin for stage III colon cancer treatment. We showed that for this case if only DFS and costs are considered as relevant outcomes, the data observation could have been stopped after 1 or at most 2 years, or even should not have started at all, at least for the purpose of informing the reimbursement decision. Our study reinforces that setting up and continuation of a registry requires regular careful assessment of its results versus the expected outcomes.

The setting of our study is similar to what has been called the adopt and trial approach [13], in which the new medication is adopted while more research is conducted to find new evidence, usually by means of a clinical trial with certain size and fixed final time. Several studies have used the VOI analysis to find the optimal design of clinical trials (e.g., [13,14,16–19]), in particular for the adopt and trial situation [13,14]. Bayesian techniques have also been widely used in sample size determination [20–22]. In contrast to the above methods, the present study evaluates the optimal time to extract specific data from a given registry with a

known design. That is, rather than the sample size, or the combination of sample size and follow-up time, the present study focuses on the follow-up time of the registry, assuming that the sample size follows from the given registry design. Although it is theoretically superior to determine both sample size and follow-up time together, in practice this is intractable for more than two periods [16,18]. Regardless of the design of the study, the basic idea to evaluate the data-gathering process remains the trade-off that is to be made between the gains of waiting for more information and the losses resulting from a delayed decision.

Another related approach is the real options approach, which has been applied in various applications, investment decisions regarding imaging techniques [23], and medical decision making in risky surgery [24]. Usually, however, an analytical solution can be obtained only by imposing strict assumptions on the distributions of the parameters involved that will not be met in practice. Especially interdependence of outcomes over time (as present in the current data set) is a problem.

The method proposed in the present study takes into account the VOI provided by additional observations as well as its costs. In valuing the information it evaluates how this information will enhance the decision to be taken on the basis of registry data. In that sense it differs from the usual considerations in registry design (e.g., data sources, patient selection, comparison groups, and sampling strategies) [25].

Using VOI methods for evaluation of data-gathering procedures during an AED process is consistent with a more general decision-making approach to decision making concerning AED. Chalkidou et al. [26] present a structured framework for this. To choose the correct access strategy using evidence-based decision making, four distinct but connected questions need to be answered: 1) Does current evidence suggest that the innovation is better than current practice? 2) Is further research worthwhile? and 3) Should a definite decision be delayed until more information becomes available? The present article adds a fourth and related question 4) What is the best time for reevaluation? To address question 2, VOI analysis is helpful. This may be either a simple expected value of perfect information to show that further research is not worthwhile or a more elaborate analysis, to investigate whether certain types of research are worth their costs. Once it turns out that further research is worthwhile, the next question must be addressed. Questions 3 and 4 are related, in the sense that if 3 implies that a definite decision should not be delayed, this means that the best time for reevaluation is now (that is a zero delay). However, when delay is appropriate, the next question is by how much.

Although the original framework leaves out this fourth question, it has been addressed by Eckerman and Willan [13] in a setting with randomized trials being used for gathering

**Table 4 – Specifications of estimates at the start point of the conditional reimbursement period ( $t_0$ ).**

Estimated input	Mean $\pm$ SD	Reference
FL + oxaliplatin survival days	900 $\pm$ 270	[12]
FL survival days	870 $\pm$ 300	[12]
Additional survival days gained by oxaliplatin	30 $\pm$ 390	[12]
Additional costs of oxaliplatin	12,500 $\pm$ 720	Expert opinion
FL, fluorouracil.		

**Table 5 – ENGs of delaying the decision after each year (numbers are rounded).**

Year	Expected gains	Total costs	ENG <sup>*</sup>	Cumulative ENG
2006	0	81,800	–81,800	–81,800
2007	0	77,400	–77,400	–159,200
2008	0	77,400	–77,400	–236,600
2009	0	77,400	–77,400	–314,000
2010	0	77,400	–77,400	–391,400
2011	0	77,400	–77,400	–468,800
2012	0	77,400	–77,400	–546,200

ENG, expected net gain.

\* Number of patients and willingness-to-pay value used for calculations are reported in Table 3.

additional information. In our study, we present a method to answer questions 3 and 4 simultaneously, assuming a registry is going on to provide the answer to these questions.

In theory, a more comprehensive approach may be to start with the complete disease model (usually a Markov model) used for the initial decision at  $t_0$  (hence when addressing question 1 in the above-mentioned framework), parameterizing all relevant uncertainties and resulting in an estimated INB. To update the INB in each stage/period would then involve using the registry data available at that moment to reestimate all relevant parameters and redo the model calculations to find a new INB. This may be quite time consuming. In the present article, we simplified the procedure by applying a simplified disease model containing only two distributions for survival and costs to result in an approximate INB. For the purpose of setting the best follow-up time, such a simplified model focusing on the most relevant parameters is handy because it allows easier reestimation. The selection of the most relevant parameters could be informed by a sensitivity analysis performed on the full disease model including a VOI analysis. If this VOI analysis (to be conducted to answer question 2 of the framework) indicates that other parameters than costs and survival are more relevant for informing the reevaluation, then a different model for calculating approximate INBs in each stage might be needed. Whatever disease model is applied, the general approach remains the same: repeatedly estimate the INB and evaluate how the new data add to its precision.

The aims that the registry is meant to support must be well defined beforehand. For example, the aim might be to gather information on implementation issues in daily care such as actual treatment costs or survivals. It might also be supporting a better informed decision on effectiveness or other outcomes for patients. Very often registries are designed to inform more than one parameter. For instance, the real-world data studied in the present article have been shown to be very helpful in comparing

guidelines to daily practice with respect to treatment choice [10]. When a registry is aiming to provide information on conditional reimbursement decisions, the requirements of such decision must be met (e.g., the outcome measurement and perspective).

Our model, however, focuses on one specific decision objective (INB) in this case, covering two parameters (DFS and medical costs). The INB was considered the most relevant outcome for a reimbursement decision and hence taken as the outcome of interest for the issue of timing the reevaluation. Quality-adjusted life-years gained would have been a worthwhile alternative health benefit measure; however, too little information was available to calculate these. Our method would not change substantially when using quality-adjusted life-years rather than life-days gained as an outcome. That is, the example may be generalized to other outcomes. The method does require a net benefit to be calculated but is not specific about what outcomes are used to calculate this net benefit.

Our approach allows comparing two treatments only because it uses INBs. For the conditional reimbursement setting, comparing two treatments is quite relevant, with one of the treatments being the new drug and the other reflecting the care as usual, possibly a mixture of treatments.

Like any observational study, registry data are inevitably biased. Although solutions for this exist, for the real-world data used in the present study, patient heterogeneity turned out to be too large to allow for appropriate correction of confounding in the registry data. This resulted in problems in estimating incremental cost-effectiveness using the registry data only [27]. As a solution, a recent study [28] has combined the registry data with the data from the MOSAIC trial [12] and the long-term follow-up data of the trial [29] to find the cost-effectiveness of oxaliplatin. Our present case study is intended to illustrate the approach and hence we did not explicitly deal with these biases in the data and just presented the uncorrected outcomes. In real-world applications, proper corrections should be included. Alternatively for

**Table 6 – Sensitivity analysis.**

Parameter	Base-case assumption/value	Assumption/value in sensitivity analysis	Optimal registry time in sensitivity analysis (y)
Willingness to pay	€60,000/DFLY	€20,000/DFLY	1
		€40,000/DFLY	1
		€80,000/DFLY	1
		€100,000/DFLY	2
Prior distribution	$\sim N(-7500, 1370^2)$	$\sim N(0, 10000^2)$	2
Prevalence proportion	0.052% (2006)	0.065% (2012)	1
Incidence proportion	0.012%	0.014% (2012)	1

DFLY, disease-free life-year.

cases that do not allow correction, the data could be used to confirm outcomes for the intervention arm only, rather than the INB. That would result in net benefits being updated. It should be noted that even if the registry data can be successfully corrected for bias, it might not yet be worthwhile to gather additional data from it. Initiation and continuation of a registry is costly, and if the gain in information is small for the purpose(s) that the registry is meant to achieve, it is better to stop the registry and avoid extra costs or not to start it at all.

The registry evaluation was modeled as a so-called wait-and-see process. In this approach, the data gathering is stopped once a low (negative) registry net gain value is observed. This implies that a decision concerning registry continuation or cessation will be taken after the registry has already started. Hence, an a priori clear idea of the duration of the registry would not be available. Generally, one would strive to make the definite reimbursement decision right after the optimal length of the observation period, that is, when the amount of information contained has been achieved and processed. This length will change for different drugs and conditions, and though the procedures followed would be clear, their timing may be indeterminate. This might cause inconvenience for the policymaker, registry researchers, and producers applying for reimbursement. One way to avoid this problem might be to use simulation at  $t_0$  and determine the optimal registry length a priori. Using an entirely simulated data set, however, would increase the uncertainty in the results. In practice, a balance will have to be struck between well-informed decisions (requiring a long actual follow-up time) and timely reconsideration of the length of follow-up.

To conclude, the present article described a way to approach registries by regular reevaluation determining the best time for a definite decision concerning reimbursement. Its findings underline that patient registries should not be considered a standard recipe for all AED procedures. Rather, they require careful design and should be used in the proper population and for the proper period, answering the proper research question. Continuation of the registry to support a reimbursement decision while it is generating little gain in information can cause losses; hence, it is essential to track its gains from the start and regularly reevaluate it.

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## Supplemental Materials

Supplementary material accompanying this article can be found in the online version as a hyperlink at <http://dx.doi.org/10.1016/j.jval.2014.10.008> or, if a hard copy of article, at [www.valueinhealthjournal.com/issues](http://www.valueinhealthjournal.com/issues) (select volume, issue, and article).

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